A Retrospective Investigation of the Relationship between Neuroblastoma Response to Cancer Therapy and Exposure to Opioids for Pain Management

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Abstract

ABSTRACT Objective: Recent increased awareness and research studies reflect possible associations between opioid exposure and cancer outcomes. Children with neuroblastoma (NB) often require opioid treatment for pain. However, associations between tumor response to chemotherapy and opioid exposure have not been investigated in clinical settings. Methods: This is a single institution retrospective review of patients with NB treated between 2013 and 2016. We evaluated opioid consumption quantified in morphine equivalent doses (mg/kg) based on nurse- or patient-controlled analgesia during antibody infusions. We also analyzed their associations with change in tumor volume and extra-adrenal tumor burden. Results: Of 42 patients given opioids for pain related to anti-GD2 mAb, data completion was achieved for 36 and details of statistical analyses were entered. Median total weight-based morphine equivalent (over 8 days) was 4.71 mg/kg (interquartile range 3.49-7.96). We found a statistically insignificant weak negative relationship between total weight-based morphine equivalents and tumor volume ratio (correlation coefficient -0.0103, p-value 0.9525) and a statistically insignificant weak positive relationship between total weight-based morphine equivalent and Curie score (correlation coefficient 0.1096, p-value 0.5247). Conclusion: Our study found no statistically significant correlation between opioid consumption and NK cell-mediated killing of NB cells as measured by effects on tumor volume/tumor load.

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Abbreviation	Full Term
antiGD2-mAb	Anti-disialoganglioside monoclonal antibodies
NB	Neuroblastoma
MRD	Minimal residual disease
PCA	Patient-controlled analgesia
MOR	Mu opioid receptor
NK cells	Natural killer cells
GTV	Gross tumor volume
MIBG	Meta-iodobenzylguanidine

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Conclusion: Our study found no statistically significant correlation between opioid consumption and NK cell-mediated killing of NB cells as measured by effects on tumor volume/tumor load.

INTRODUCTION

Opioid therapy is the cornerstone of pain treatment for patients with cancer.[1] Increased awareness of the potential impact of opioids on the immune system and oncological outcomes has been developing, particularly

in the context of newer chemotherapy agents that engage the body's immune system in the fight against cancer cells.[2] Cancer treatment has entered an era of immunotherapy,[3] and newly-designed immunotherapies harness the immune system to fight cancer cells.

NB is the most common extracranial solid tumor in childhood.[4] Standard therapy for NB has historically consisted of three phases of treatment: (1) induction with intensive multi-agent chemotherapy; (2) consolidation with myeloablative therapy and stem cell rescue; and (3) treatment of minimal residual disease (MRD) with isotretinoin.[5] However, after a period of regression, patients may experience a recurrence secondary to drug-resistant cancer cells. Researchers have postulated that more effective treatment of MRD with anti-disialoganglioside monoclonal antibodies (antiGD2-mAb) would reduce the rate of recurrence.[5-8] NB cells show a uniform expression of GD2 receptors on their surface, whereas there is a minimal presence of GD2 receptors on some non-tumor cells (predominantly neurons, melanocytes, and peripheral sensory nerve fibers).[5-7]Dinutuximab and Naxitimab, two antiGD2-mAbs, are immunotherapy agents used in the treatment of neuroblastoma (NB).[9] The use of anti-GD2 mAb has become the standard of care in the treatment of NB. The initial form of this mAb (ch14.18) was partly murine (i.e. chimeric) and caused significant pain in patients during intravenous infusion.[5,8] A second-generation antibody hu14.18 (humanized) was developed to reduce the adverse effects of the chimeric antibody.[8,10] A point mutation was inserted in a newer anti-GD2 mAb (hu14.18K322A) to reduce complement-mediated pain, as research suggested that complement pathway activation played a significant role in pain development.[8,11] Although higher doses of the mAb are now tolerated following this mutation, pain is still common[10] given the ongoing binding of mAb to normal peripheral sensory nerve fibers.[5,12]

An effective approach to the treatment of anti-GD2 mAb-related pain has been opioid patient/controlled analgesia (PCA) administered as a parenteral opioid infusion prior to initiation of anti-GD2 mAb and continued throughout the mAb infusion.[10] However, there is reason to be skeptical with the use of opioids in this setting. Research has brought to light the potential interaction of opioid analgesics with the proliferation of cancer cells.[13,14] Although the clinical significance of in vitro data have been inconclusive to date, it is clear that opioids modulate the immune system and have an in vitro effect on cancer cells. It appears that both endogenous and exogenous opioids can stimulate angiogenesis, thus prompting enhanced tumor growth and metastasis.[14] This has implications for both primary treatment and treatment of MRD and later metastatic disease. Studies have demonstrated an upregulation of the mu opioid receptor (MOR) on tumor cells. Lennon et al. evaluated MOR expression in non-small cell lung cancer tissue and found that cells having MOR overexpression had a 2.5-fold increase in primary tumor growth rate compared to control cells.[14] Multiple theories on the effect of opioids on immunity have been postulated, including stimulation of epithelial-mesenchymal transformation and an inhibitory effect on both innate and acquired immune responses, specifically natural killer (NK) cells,[15,16] as well as decreasing phagocytic functioning of granulocytes.[17] In preclinical and animal studies, morphine and fentanyl have been shown to reduce NK cell activity, the main cellular defense against oncogenic cells.[16,18,19] Anti-GD2 mAb relies on NK cells as the effector cells of NB tumor cell killing.[6,7] Therefore, suppression of NK cell activity could theoretically decrease the efficacy of anti-GD2 mAb treatment.

This study assessed the possible impact of opioids on the effectiveness of anti-GD2 mAb (hu14.18K322A) in facilitating the eradication of NB cells. We performed a retrospective review of medical records of patients undergoing NB treatment as part of an institutional phase II clinical trial.[20] Patients on the clinical trial receive two identical courses of chemoimmunotherapy and then their tumor response is assessed by imaging. This study will attempt to determine the impact of opioids on tumor response using two outcome measures: 1) cumulative opioid consumption (mg/kg) and 2) degree of tumor reduction (primary tumor volume and extra-primary location tumor burden as determined by the Curie score) during the first two courses of induction chemoimmunotherapy. These measures will be used to assess the relationship between opioid exposure and tumor reduction response to chemotherapy.

METHODS

2.1 PATIENTS

We conducted a retrospective review of patients with NB treated at a single institution between 2013 and 2016. The study was approved by the Institutional Review Board.

2.2 DEMOGRAPHIC VARIABLES

Demographic variables collected were age, sex, race, weight, and height.

2.3 OPIOID CONSUMPTION

Medical records were reviewed to determine the type and amount of opioid administered during two inpatient admissions for anti-GD2 mAb infusion. Anti-GD2 mAb was infused during two inpatient admissions for induction chemotherapy as follows:

Course 1: Daily for 4 days (days 2 through 5 of induction chemotherapy)

Course 2: Daily for 4 days (days 22 through 25 of induction chemotherapy)

During the 8 days (two distinct four-day infusions), patients received an opioid infusion and bolus doses (morphine, hydromorphone, or fentanyl) as PCA. Opioid consumption was quantified in morphine equivalent doses (mg/kg) and summated for the two 4-day time intervals, respectively.

Gross Tumor Volume and Metastases Evaluations

Prior to course 1, imaging examinations by magnetic resonance imaging (MRI) and/or computed tomography (CT) were performed to quantify the gross tumor volume (GTV, in cm^3) of the primary NB tumor. Imaging examinations were repeated after course 2 of antibody infusions to obtain a new GTV following induction chemotherapy. These volumes were available from the institutional NB study database. A "tumor volume ratio" was calculated by dividing the GTV prior to course 1 by the GTV following course 2. A greater treatment response led to smaller GTV following course 2 (smaller denominator) and therefore a higher tumor volume ratio. In the absence of response, both the numerator and denominator of the tumor volume ratio are the initial GTV, which led to a tumor volume ratio of 1. For patients with a*complete* response to treatment (2^{nd} GTV essentially 0 cm^3), the denominator of the tumor volume ratio was credited as "1 cm^3" to prevent an undefined fraction. To summarize, a higher tumor volume ratio equated to a greater response to treatment. A tumor volume ratio of 1 equated to a complete *lack* of response to treatment.

Additionally, tumor burden *outside* of the primary tumor was evaluated using Curie scores obtained by meta-iodobenzylguanidine (MIBG) scans.[21] A Curie score ratio (Curie score prior to course 1 divided by Curie score following course 2) was calculated and used for analysis rather than raw Curie scores.

2.4 STATISTICAL ANALYSES

Patient characteristics were summarized by descriptive statistics. Spearman's Rank Correlation Coefficient was utilized to examine the relationship between total weight-based morphine equivalents and tumor response. Tumor response was assessed by two measurements: tumor volume ratio (GTV prior to course 1 divided by GTV following course 2) and Curie score ratio after two cycles of therapy. We studied associations of demographic variables (age, sex, race) with opioid exposure variables (total weight-based morphine equivalents), as well as with outcome variables (tumor volume ratio and Curie score ratio). Because these associations were found insignificant, multivariate analyses adjusting for age, sex, and race were not conducted. Statistical analyses were conducted using SAS software Version 9.4 (SAS Institute, Cary, NC). A two-sided significance level of $P<0.05$ was considered statistically significant.

RESULTS

DESCRIPTION OF PATIENT POPULATION

Forty-two patients were treated with anti-GD2 mAb during the study period. Three patients were excluded as they had complete surgical excision prior to course 2. For these patients, tumor volume ratio was incalculable and response to treatment could not be attributed to chemotherapy alone. Three additional patients were excluded from analysis for the following reasons: one did not complete mAb therapy; one underwent

concurrent radiation therapy; and one was intubated, mechanically ventilated, and sedated with propofol for the period of the mAb infusion secondary to respiratory failure. Demographic and clinical characteristics of the remaining 36 patients are shown in Table 1. The median age was 6 years (interquartile range 4-7). The majority of patients were male (55.56%), having a median weight of 15.20 kg (interquartile range 13.05-18.60), of white race (72.22%), and were initially given morphine (88.89%). The median total weight-based morphine equivalent (over 8 days) was 4.71 mg/kg (interquartile range 3.49-7.96). Seventeen patients had a change in treatment to a second opioid (opioid rotation) at some point during either of the two 4-day cycles, either for intolerable side effects or lack of analgesic efficacy of the initial opioid chosen. In this circumstance, the secondary opioid was converted to morphine equivalent doses and added to the initial morphine doses to establish an overall opioid consumption in morphine equivalent doses (mg/kg).

3.2 RELATIONSHIP BETWEEN EXPOSURE TO OPIOIDS AND TUMOR RESPONSE

Spearman's Rank Correlation coefficient was performed to determine the strength and direction of the linear relationship between the total weight-based morphine equivalents and tumor response. The correlation coefficient of -0.0103 and P-value of 0.9525 indicates a statistically insignificant, weak negative relationship between total weight-based morphine equivalents and tumor volume ratio (Figure 1). The correlation coefficient of 0.1096 and p-value 0.5247 indicates statistically insignificant weak positive relationship between total weight-based morphine equivalent and Curie score (Figure 2).

DISCUSSION

The impact of opioids on cancer outcomes has been an ongoing topic of considerable debate and investigation.[22-26]Cell-mediated immunity is critical for the eradication of tumor cells and prevention of metastases development.[27,28]Multiple preclinical studies have demonstrated the suppressive effects of opioids on the immune system in general and NK cells specifically,[18,22-25,29] but this effect is variable amongst different types of opioids.[22] Clinical studies have been equivocal and results are inconsistent across different types of cancers.[2,30,31] This observation likely suggests that the impact (if any), is unique to certain subtypes of cancer and cannot be applied to cancer generally. For this reason, it is important to investigate the impact of opioids on cancer outcomes within specific diagnoses, such as NB. It is known that NB treatment with anti-GD2 mAb relies on NK cells as the effector cells of the tumor cell killing.[6,7] Therefore, one would expect that increased opioid consumption would correlate with decreased tumor killing.

Our findings did not conclusively support the general hypothesis that the magnitude of opioid exposure negatively impacts anti-GD2 mAb-directed tumor reduction. However, this does not indicate that there is no correlation, as we did find a weakly negative correlation (as hypothesized) between primary tumor volume reduction and total weight-based morphine equivalents. Interestingly, we found the opposite correlation (weakly positive) between tumor reduction outside the primary tumor (as measured by Curie score) and total weight-based morphine equivalents. This was the opposite of what was hypothesized. However, neither measure achieved statistical significance. It is likely that the impact on tumor reduction may be too minimal to be detected by our study methodology. While the study design is novel (the use of tumor reduction as a marker of opioid impact on chemotherapy effectiveness), it may not be sensitive enough. If opioids suppress NK cell activity in vivo, as seen in vitro, the clinical significance is likely too minimal to be detected by tumor volume reduction at the primary tumor site or other locations. The current anti-tumor therapies may be effective enough that small variations in the tumor response in relationship to opioid exposure may not be detected by this study design and with this small sample size. Still, this study design is unique in that it investigated the impact of more than just a single perioperative opioid exposure, as is the design seen in most investigations of the impact of opioid/anesthesia on cancer outcomes.[30-33] While the opioid exposure in this study was more than perioperative, it can still be classified as an *acute* opioid exposure (8 total days). It is possible that since there is a different mechanism by which acute versus chronic opioid administration modulates the immune system,[15,16] the duration of opioid therapy in our patient population did not have as significant an impact on their tumor progression as a patient population with a more chronic exposure to opioid therapy would have.

Not only does the impact of opioids on cancer likely vary with duration of opioid exposure, but also opioid dose. Studies have shown that higher doses of morphine affect NK cells differently than do lower doses. Higher doses lose specificity for MOR and can bind to delta opioid receptors, which may *increase* NK cell activity.[15,16]

A potential limitation of this study may be the lack of accounting for differences in immunosuppression by opioid *type* , as all opioid doses were converted to morphine equivalent doses. Justifiably, this choice was based on the small number of patients and occurrences of pain treatment with opioids other than morphine. It is known that different drugs within the opioid class inhibit NK cells to different degrees[16,22] and our study was not powered enough to detect differences based on the type of opioid used. Finally, another potential limitation of this study is related to the role of interleukin-2 (IL-2). All patients on the institutional protocol received IL-2 on days following the anti-GD2 mAb infusion (following course 1 and course 2), which has a pro-NK cell effect.[34] It is conceivable that the pro-NK cell effect of the IL-2 counteracted or masked any potential anti-NK cell effect of the opioid.

Although our results do not suggest a clinically significant correlation between opioids converted to morphine equivalent doses and adverse effects on tumor reduction, it should not be presumed that opioids can be used without limitation. The warnings from preclinical studies that demonstrate the immunosuppressive effects of opioids can be heeded without compromising patient care. It may be prudent to favor the use of opioids that have been shown to cause lesser degrees of immunosuppression (e.g., hydromorphone, oxycodone, tramadol).[16,22] Additionally, it is advisable to maximize the use of non-opioid analgesics to minimize opioid consumption, particularly if a non-opioid analgesic such as lidocaine has been shown to have anti-tumor effects.[35-38] This approach to the management of pain associated with anti-GD2 mAb has been demonstrated previously.[12] Gorges et al. reported that dexmedetomidine and hydromorphone (both drugs that are not known to affect NK cells) can be safely and effectively used to treat pain in this patient population.[12] Regardless, the effective treatment of pain is essential as untreated pain shows similar immunosuppressive effects.[39,40]

In conclusion, our study did not find a statistically significant correlation between the consumption of opioids and the NK cell mediated killing of NB cells as measured by effects on tumor volume/tumor load. Although our findings do not endorse indiscriminate or excessive opioid utilization, it is reassuring that the doses used in this study to ameliorate the severe pain that accompanies antibody treatment do not have adverse effects on tumor response to antibody. Opioid sparing measures can and should be employed, when possible, given the untoward secondary effects of prolonged opioid use, regardless of any potentially negative influence on cancer biology.

CONFLICTS OF INTERESTS

The authors report no conflicting interests.

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LEGENDS

Figure 1. Scatter plot of total weight-based morphine equivalent and tumor volume ratio

Figure 2. Scatter plot of total weight-based morphine equivalent and Curie Score

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`Table 1.docx` available at https://authorea.com/users/481870/articles/568690-a-retrospective-investigation-of-the-relationship-between-neuroblastoma-response-to-cancer-therapy-and-exposure-to-opioids-for-pain-management

Figure 1. Scatter plot of total weight-based morphine equivalent and tumor volume ratio

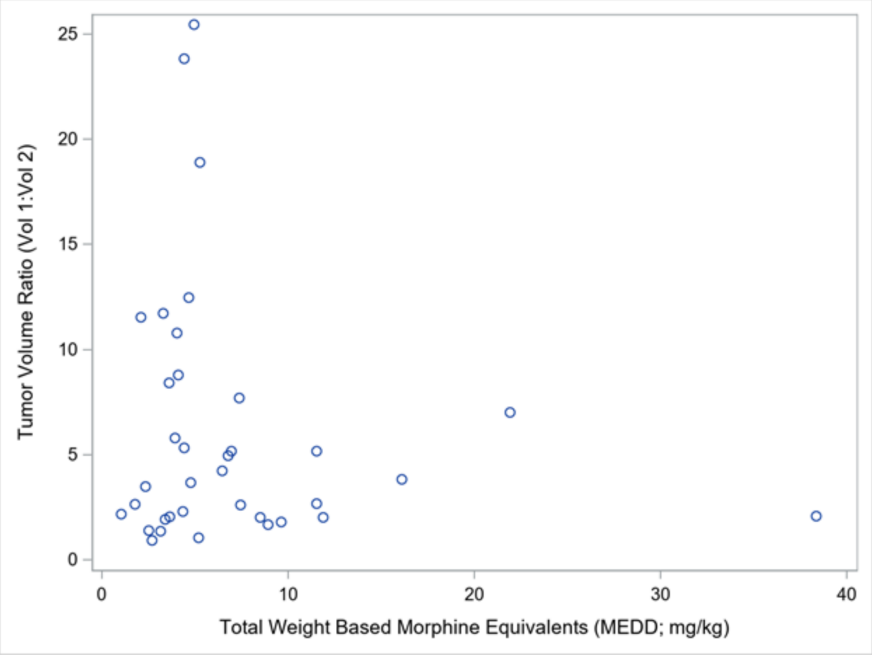

Figure 2. Scatter plot of total weight-based morphine equivalent and Curie Score